PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/415 | A1

(11) International Publication Number: WO 96/19991

(43) International Publication Date: 4 July 1996 (04.07.96)

(21) International Application Number: PCT/EP95/05172

(22) International Filing Date: 21 December 1995 (21.12.95)

(30) Priority Data:
94203774.8 28 December 1994 (28.12.94) EP
(34) Countries for which the regional or international application was filed: DE et al.

(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

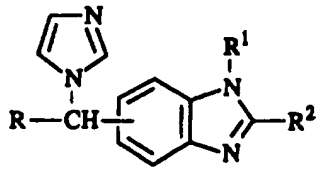
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: VANDEN BOSSCHE, Hugo, Florent, Adolf [BE/BE]; Steenweg op Gierle 68, B-2300 Turnhout (BE). WILLEMSENS, Gustaaf, Henri, Maria [BE/BE]; Stekelbaarsstraat 24, B-2340 Beerse (BE). DE COSTER, Roland [BE/BE]; Gestelbos 26, B-2980 Zoersel (BE).

(81) Designated States: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: BENZIMIDAZOLES AS INHIBITORS OF CALCITRIOL METABOLISM

(57) Abstract



(I)

The invention relates to the use of a (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazole, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, for the manufacture of a medicament for treating a pathological condition which is beneficially influenced by inhibiting the metabolic degradation of calcitriol, said benzimidazole having formula (I), wherein R is hydrogen; C_{1-10}alkyl; C_{3-7}cycloalkyl; Ar^1 or Ar^1-C_{1-6}alkyl; R^1 is hydrogen; C_{3-7}cycloalkyl; Ar^1; C_{1-10}alkyl; C_{1-6}alkyl substituted with Ar^1 or C_{3-7}cycloalkyl; hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{3-6}alkenyloxy optionally substituted with Ar^2; C_{3-6}alkynyloxy optionally substituted with Ar^2; or Ar^1-oxy; R^2 is hydrogen; halo; C_{1-10}alkyl; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; Ar^1; quinolinyl; indolinyl; C_{1-6}alkyl substituted with Ar^1, C_{3-7}cycloalkyl, quinolinyl, indolinyl or hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{3-6}alkenyl optionally substituted with Ar^1; Ar^2-oxy; C_{1-6}alkyloxycarbonyl; carboxyl; C_{1-6}alkylcarbonyl; Ar^1-carbonyl or Ar^1-(CHOH)-; compositions comprising calcitriol or a prodrug thereof and a compound of formula (I).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

BENZIMIDAZOLES AS INHIBITORS OF CALCITRIOL METABOLISM

The present invention is concerned with the use of (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazoles for the manufacture of a medicament for treating a pathological condition which is beneficially influenced by inhibiting the metabolic degradation of calcitriol.

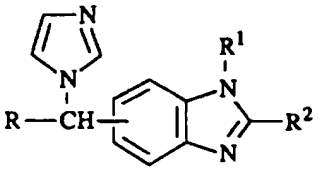
Calcitriol (generic to 1α,25-dihydroxy-vitamin D_3) is endogenously formed from vitamin D_3 by metabolic reactions and appears to carry out all the functions attributed to the vitamin D hormone system. Vitamin D compounds are involved in the regulation of calcium and phosphate homeostasis and bone mineralisation. The daily requirements of vitamin D are met by exposure to sunlight and/or obtained from the diet. In case of inadequate exposure to sunlight and/or a lack of the vitamin in the diet, problems of vitamin D deficiency may arise. These problems are further aggravated by the rapid metabolism of calcitriol to inactive compounds.

Further, calcitriol has been described to show antiinflammatory and immunomodulating activity. It has also been shown that calcitriol stimulates the differentiation of cells and has inhibitory activity on cell proliferation. Moreover, the compound has potential use in the treatment of hypertension and diabetes mellitus. The therapeutic potential of exogenously administered calcitriol, however, is limited by its rapid metabolic degradation. Furthermore, excessive intake of the compound leads to the development of adverse effects.

(1*H*-imidazol-1-yl)methyl-1*H*-benzimidazoles have been described in EP-0,260,744 having inhibitory activity on androgen formation and are useful in preventing or therapeutically treating androgenic hormone dependent disorders. EP-0,371,559 discloses the use of these compounds to suppress the metabolism of retinoids. Said property can be used to control the rate of growth and differentiation of normal, preneoplastic and neoplastic epithelial cells, thus making these compounds useful in the treatment of carcinoma and keratinization disorders. The (+) isomer of 5-[3-chlorophenyl]-1*H*-imidazol-1-ylmethyl]-1*H*-benzimidazole has been described in WO 95/22540, published on August 24, 1995, as being particularly useful in the field of dermatology. The (-) isomer of 5-[3-chlorophenyl]-1*H*-imidazol-1-ylmethyl]-1*H*-benzimidazole has been described in WO 95/22541, published on August 24, 1995, as being particularly useful in the field of oncology.

Quite unexpectedly, the (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazoles described in the present invention inhibit the metabolic degradation of calcitriol and overcome certain problems associated with art known vitamin D therapy.

The present invention relates to the use of (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazoles, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, for the manufacture of a medicament for treating a pathological condition which is beneficially influenced by inhibiting the metabolic degradation of calcitriol, said benzimidazoles having the formula



(I),

wherein

R is hydrogen; C_{1-10}alkyl; C_{3-7}cycloalkyl; Ar^1 or Ar^1-C_{1-6}alkyl;

R^1 is hydrogen; C_{3-7}cycloalkyl; Ar^1; C_{1-10}alkyl; C_{1-6}alkyl substituted with Ar^1 or C_{3-7}cycloalkyl; hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{3-6}alkenyloxy optionally substituted with Ar^2; C_{3-6}alkynyloxy optionally substituted with Ar^2; or Ar^1-oxy;

R^2 is hydrogen; halo; C_{1-10}alkyl; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; Ar^1; quinolinyl; indolinyl; C_{1-6}alkyl substituted with Ar^1, C_{3-7}cycloalkyl, quinolinyl, indolinyl or hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{3-6}alkenyl optionally substituted with Ar^1; Ar^2-oxy; C_{1-6}alkyloxycarbonyl; carboxyl; C_{1-6}alkylcarbonyl; Ar^1-carbonyl or Ar^1-(CHOH)-;

each Ar^1 independently is phenyl, substituted phenyl, pyridinyl, aminopyridinyl, imidazolyl, thienyl, halothienyl, furanyl, halofuranyl or thiazolyl;

each Ar^2 independently is phenyl or substituted phenyl;

in Ar^1 and Ar^2 said substituted phenyl represents phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, amino, mono- and di(C_{1-6}alkyl)amino, nitro, carboxyl, formyl and C_{1-6}alkyloxycarbonyl.

As used in the foregoing definitions the term halo is generic to fluoro, chloro, bromo and iodo; the term "C_{1-4}alkyl" is meant to include straight and branch chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl and the like;

"C_{1-6}alkyl" includes C_{1-4}alkyl radicals and the higher homologs thereof having 5 or 6 carbon atoms; "C_{1-10}alkyl" is meant to include C_{1-6}alkyl radicals, as defined hereinabove, and the higher homologs thereof having from 7 to 10 carbon atoms; the term "C_{3-7}cycloalkyl" is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; "C_{3-6}alkenyl" defines straight chained and branched hydrocarbon radicals containing one double bond having from 3 to 6 carbon atoms such as, for example, 3-propenyl, 2-butenyl and the like; "C_{3-6}alkynyl" defines straight chained and branched hydrocarbon radicals containing one triple bond and having from 3 to 6 carbon atoms such as, for example, 3-propynyl, 2-butynyl and the like; and when a C_{3-6}alkenyl or a C_{3-6}alkynyl is substituted on a heteroatom, then the carbon atom of said C_{3-6}alkenyl or said C_{3-6}alkynyl connected to said heteroatom preferably is saturated.

The addition salts as mentioned herein are meant to comprise the therapeutically active addition salt forms which the compounds of formula (I) are able to form with appropriate acids, such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

The pharmaceutically acceptable addition salts as mentioned hereinabove are also meant to comprise the therapeutically active non-toxic base, in particular, a metal or amine addition salt forms which the compounds of formula (I) are able to form. Said salts can conveniently be obtained by treating the compounds of formula (I) containing acidic hydrogen atoms with appropriate organic and inorganic bases such as, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted by treatment with an appropriate base or acid into the free acid or base form.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) are able to form and said solvates are meant to be included within the scope of the present invention. Examples of such solvates are, e.g. the hydrates, alcoholates and the like.

The compounds of formula (I) wherein R is other than hydrogen have an asymmetric carbon atom in their structure, the absolute configuration of which may be represented by the descriptors R and S. Formula (I) is intended to encompass all enantiomers and diastereoisomers of the compounds of the invention as well as the mixtures thereof, in particular the racemates and the enantiomerically pure forms (i.e. the enantiomeric excess is equal to or higher than 95%).
Further, the compounds of formula (I) may contain in their structure a tautomeric system and, consequently, these compounds can be represented by each of their tautomeric forms. All tautomeric forms are meant to be embraced by the definition of the compounds of formula (I).

In particular, the present invention is concerned with the use of a compound of formula (I) wherein R is phenyl or substituted phenyl; R^1 is hydrogen or C_{1-6}alkyl; R^2 is hydrogen; halo; C_{1-6}alkyl; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; phenyl; substituted phenyl; C_{1-6}alkyl substituted with phenyl or substituted phenyl; said substituted phenyl representing phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy and cyano.

Interesting compounds within the invention are the compounds of formula (I) wherein the 1*H*-imidazol-1-ylmethyl moiety is substituted on either the 4, 5, 6 or 7 position of the benzimidazole ring.

More interesting compounds are the compounds of formula (I) wherein the 1*H*-imidazol-1-ylmethyl moiety is substituted on either the 5 or 6 position of the benzimidazole ring.

Another group of interesting compounds within the present invention are those compounds wherein R^1 is hydrogen; and R^2 is hydrogen, C_{1-6}alkyl or phenyl.

The preferred compounds within the invention are (±)-5-[(3-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-benzimidazole (generically known as liarozole), (+)-liarozole, (-) liarozole and the pharmaceutically acceptable addition salts thereof, in particular, the hydrochloride and the fumarate salts such as, for example, liarozole hydrochloride, liarozole fumarate, (+)-liarozole hydrochloride and (-)-liarozole hydrochloride.

The preparation of the compounds of formula (I) is described in EP-0,260,744, EP-0,371,559, WO 95/22540 and WO 95/22541.

Vitamin D_3 is sequentially metabolized by enzymes, first to 25-hydroxy-vitamin D_3 in the liver and then to either 24,25-dihydroxy-vitamin D_3 or the active hormonal form 1α,25-dihydroxy-vitamin D_3 in the kidney. Vitamin D_3 (generically known as cholecalciferol) and 25-hydroxy-vitamin D_3 (generically known as calcifediol), therefore, are prodrugs of the subject active compound calcitriol. Another prodrug of calcitriol is 1α-hydroxy-vitamin D_3 (generically known as alfacalcidol), which is hydroxylated at the 25 position in the liver to give calcitriol. Calcitriol is further metabolized to inactive degradation products, e.g. in the kidney and the skin. The compounds of formula (I) are useful in inhibiting the metabolic degradation of endogenously formed and exogenously administered calcitriol. The inhibitory activity of the compounds of formula (I) on the metabolic degradation of calcitriol is evidenced by measuring the impact of said compounds on the calcitriol degradation in human foreskin keratinocytes, pig kidney cells and human hepatoma cells, as described hereinafter.

In view of the useful inhibitory activity of the compounds of formula (I) on the metabolic degradation of calcitriol, the therapeutic potential of the compounds of formula (I), optionally in combination with calcitriol or a prodrug thereof, preferably, cholecalciferol, calcifediol or alfacalcidol, extends to all pathological conditions which are beneficially influenced by inhibiting the metabolic degradation of calcitriol. For instance, the compounds of formula (I) optionally in combination with calcitriol or a prodrug thereof, preferably, cholecalciferol, calcifediol or alfacalcidol, can be useful in the treatment of vitamin D deficiency states. Vitamin D deficiency may arise from inadequate exposure to sunlight and/or from a lack of the vitamin in the diet and is further aggravated by the rapid metabolic degradation of calcitriol, and leads to a syndrome characterized by hypocalcaemia, hypophosphataemia, bone softening and bone pain. Other clinical applications of the compounds of formula (I) optionally in combination with calcitriol or a prodrug thereof, preferably, cholecalciferol, calcifediol or alfacalcidol, are reviewed by Bouillon et al., Endocrine Reviews (1995) *16(2)*, 200-257 and include metabolic bone disorders, e.g. osteoporosis, osteopetrosis and the like; primary and secundary hyperparathyroidism; renal osteodystrophy; diseases of the immune system or other conditions characterized by an abnormal interleukin production, e.g. inflammatory diseases such as rheumatoid arthritis and asthma; hypertension; diabetes mellitus; diseases characterized by abnormal cell proliferation and/or differentiation, such as cancer, e.g. leukemia, carcinoma, sarcoma, lymphoma and the like; and, in particular, keratinization disorders, e.g. acne, psoriasis, lamellar ichthyosis, plantar warts, callosities, acanthosis nigricans, lichen planus, molluscum, melasma, corneal epithelial abrasion, geographic tongue, Fox-Fordyce disease, cutaneous metastatic melanoma and

keloids, epidermolytic hyperkeratosis, Darier's disease, pityriasis rubra pilaris, congenital ichthyosiform erythroderma, hyperkeratosis palmaris et plantaris, and similar disorders. The usefulness in the treatment and/or prevention of keratinization disorders may be demonstrated in the "Vaginal Keratinazation Test in Ovariectomized Rats" (J. Pharmacol. Exper. Therap.(1992) *261(2)*, 773-779).

Thus, the present invention concerns the use of (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazoles of formula (I) for the manufacture of a medicament for treating a pathological condition which is beneficially influenced by inhibiting the metabolic degradation of calcitriol. Also, the present invention concerns a method of treating patients suffering from a pathological condition which is beneficially influenced by inhibiting the metabolic degradation of calcitriol, said method consisting of administering to a patient an effective amount of a compound of formula (I), an addition salt or a stereochemically isomeric form thereof.

Another aspect of the incvention concerns the use of (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazoles of formula (I) in combination with calcitriol or a prodrug thereof for the manufacture of a medicament for treating a pathological condition which is beneficially influenced by inhibiting the metabolic degradation of calcitriol. Also, this aspect of the invention concerns a method of treating patients suffering from a pathological condition which is beneficially influenced by inhibiting the metabolic degradation of calcitriol, in particular keratinization disorders such as psoriasis, said method consisting of administering to a patient (a) an effective amount of calcitriol or a prodrug thereof and (b) an effective amount of a compound of formula (I), an addition salt or a stereochemically isomeric form thereof.

As mentioned hereinabove, the invention relates to a single drug therapy involving a compound of formula (I), as well as a combination therapy including a compound of formula (I) and calcitriol or a prodrug thereof. For both types of therapy, the active ingredients each independently may be administered orally, rectally, percutaneously, topically or by parenteral injection, depending on the affliction to be treated and the evaluation of the physician prescribing the treatment with the subject drugs. Preferably, the drugs each independently are administered orally or topically.

In case of a combination therapy, the compounds of formula (I) and calcitriol or a prodrug thereof may be administered separately (i.e. simultaneously, concurrently or consecutively) or the different drugs may be combined in one dosage form.

A particular embodiment of the invention relates to a product containing (a) a pharmaceutical composition containing an effective amount of calcitriol or a prodrug thereof and (b) a pharmaceutical composition containing an effective amount of a compound of formula (I), an addition salt or a stereochemically isomeric form thereof, as a combined preparation for simultaneous, separate or sequential use in pathological conditions which are beneficially influenced by inhibiting the metabolic degradation of calcitriol, in particular, keratinization disorders such as psoriasis. Preferentially, the product contains (a) a pharmaceutical composition containing an effective amount of calcitriol or a prodrug thereof and (b) a pharmaceutical composition containing an effective amount of (±)-5-[(3-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-benzimidazole (generically known as liarozole), (+)-liarozole, (-) liarozole or a pharmaceutically acceptable addition salt thereof, in particular, liarozole hydrochloride, liarozole fumarate, (+)-liarozole hydrochloride and (-)-liarozole hydrochloride. Such products may comprise, for example, a kit comprising a container with a suitable composition containing calcitriol or a prodrug thereof and another container comprising a compound of formula (I), an addition salt or a stereochemically isomeric form thereof. Such a product may have the advantage that a physician can select on the basis of the diagnosis the appropriate amounts of each component and the sequence and timing of the administration thereof.

Whether or not the compounds of formula (I) and calcitriol are administered separately or together, the drugs are preferably formulated in specific compositions thereof. As appropriate compositions there may be cited all compositions usually employed for systemically or topically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which

the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs, e.g. creams, gels, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. Application of said compositions may be by aerosol, e.g. with a propellent such as nitrogen carbon dioxide, a freon, or without a propellent such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl-b-cyclodextrin. Acid or base addition salts of compounds of formula (I) due to their increased water solubility over the corresponding base or acid form, are obviously more suitable in the preparation of aqueous compositions. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions.

For systemic administration, it is advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powders packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Other such compositions are preparations of the cosmetic type, such as toilet waters, lotions, skin milks or milky lotions. Said preparations contain, besides the active ingredients, components usually employed in such preparations. Examples of such components are oils, fats, waxes, surfactants, humectants, thickening agents, antioxidants, viscosity stabilizers, chelating agents, buffers, preservatives, perfumes, dyestuffs, lower alkanols, and the like.

Apart from the above-described compositions, covers may be used, e.g. plasters, bandages, dressings, gauze pads and the like, containing an appropriate amount of a composition as referred hereinabove. In particular, covers may be applied which have been impregnated or sprinkled with a liquid formulation containing the active agents, or strewn with a powdery solid composition, or smeared, covered or coated with a semi-liquid composition.

Hence, particular compositions are those adapted for topical administration. The latter compositions comprise a skin-acceptable carrier, an effective amount of a compound of formula (I), an addition salt or a stereochemically isomeric form thereof, and an effective amount of calcitriol or a prodrug thereof.

In general it is contemplated that an effective daily dose of a compound of formula (I), an addition salt or a stereochemically isomeric form thereof would be from 0.001 mg/kg to 20 mg/kg body weight and more preferably from 0.01 mg/kg to 10 mg/kg body weight. The effective daily dose of calcitriol or a prodrug thereof ranges from about 0.1 μg to about 10 mg, in particular from about 0.5 μg to about 1 mg and preferably from about 1 μg to about 0.1 mg. It may be appropriate to administer the required dose as several sub-doses at appropriate intervals throughout the day. In particular, (+)-liarozole hydrochloride, (-)-liarozole hydrochloride or (±)-liarozole hydrochloride is suitably administered b.i.d..

Preferred compositions for topical application comprise from 0.005 to 0.5% w/w (particularly from 0.01 to 0.1%) calcitriol and/or from 0.05 to 5% of (+)-liarozole hydrochloride, (-)-liarozole hydrochloride or (±)-liarozole hydrochloride, in a semi-solid or liquid diluent or carrier. The topical compositions are applied to the area to be treated or protected at regular intervals as needed, generally about 7 to about 21 times per week. The duration of the treatment will depend upon the nature and severity of the condition to be treated as well as the frequency of application of the composition.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects.

Experimental part

A) Composition Examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for administration to warm-blooded animals in accordance with the present invention.

"Active ingredient 1" (A.I. 1) as used throughout these examples relates to a compound of formula (I), a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof. "Active ingredient 2" (A.I. 2) relates to calcitriol or a prodrug thereof. Formulations containing a single active ingredient as well as those comprising both active ingredients are exemplified.

Example 1 : ORAL SOLUTION

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxy-benzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of A.I. 1 and/or 0.2 g of A.I. 2. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propane-triol and 3 l of sorbitol 70% solution were added thereto. 40 g of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of A.I. 1 and/or 0.05 mg of A.I. 2 per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example 2: CAPSULES

20 g of A.I. 1 and/or 0.2 g of A.I. 2, 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of A.I. 1 and/or 0.2 mg of A.I. 2.

Example 3 : INJECTABLE SOLUTION

0.5 mg A.I. 1 and/or 0.05 mg A.I. 2, 50 mg glucose anhydrous and 0.332 ml concentrated hydrochloric acid were mixed with 0.8 ml water for injections. Sodium hydroxide was added until pH = 3.2 ± 0.1 and water was added to 1 ml. The solution was sterilized and filled in sterile containers.

Example 4 : 2% CREAM

75 mg stearyl alcohol, 2 mg cetyl alcohol, 20 mg sorbitan monostearate and 10 mg isopropyl myristate are introduced into a doublewall jacketed vessel and heated until the mixture has completely molten. This mixture is added to a separately prepared mixture of purified water, 200 mg propylene glycol and 15 mg polysorbate 60 having a temperature of 70 to 75°C while using a homogenizer for liquids. The resulting emulsion is allowed to cool to below 25°C while continuously mixing. A solution of 20 mg A.I. 1 and/or 0.2 mg A.I. 2, 1 mg polysorbate 80 and purified water and a solution of 2 mg sodium sulfite anhydrous in purified water are next added to the emulsion while continuously mixing.

The cream, 1 g of the A.I. 1 and/or 10 mg A.I. 2 are homogenized and filled into suitable tubes.

Example 5 : 2% TOPICAL GEL

To a solution of 200 mg hydroxypropyl β-cyclodextrine in purified water is added 20 mg A.I. 1 and/od 0.2 mg A.I. 2 while stirring. Hydrochloric acid is added until complete dissolution and then sodium hydroxide is added until pH 6.0. This solution is added to a dispersion of 10 mg carrageenan PJ in 50 mg propylene glycol while mixing. While mixing slowly, the mixture is heated to 50°C and allowed to cool to about 35°C whereupon 50 mg ethyl alcohol 95% (v/v) is added. The rest of the purified water q.s. ad 1 g is added and the mixture is mixed to homogenous.

Example 6 : 2% LIPOSOME FORMULATION

A mixture of 2 g A.I. 1 and/or 0.02 g A.I. 2 microfine, 20 g phosphatidyl choline, 5 g cholesterol and 10 g ethyl alcohol is stirred and heated at 55-60°C until complete dissolution and is added to a solution of 0.2 g methyl paraben, 0.02 g propyl paraben, 0.15 g disodium edetate and 0.3 g sodium chloride in purified water while homogenizing. 0.15 g Hydroxypropylmethylcellulose in purified water ad 100 g is added and the mixing is continued until swelling is complete.

Example 7 : 2% LIPOSOME FORMULATION

A mixture of 10 g phosphatidyl choline and 1 g cholesterol in 7.5 g ethyl alcohol is stirred and heated at 40°C until complete dissolution. 2 g A.I. 1 and/or 0.02 g A.I. 2 microfine is dissolved in purified water by mixing while heating at 40°C. The alcoholic solution is added slowly to the aqueous solution while homogenizing during 10 minutes. 1.5 g Hydroxypropylmethylcellulose in purified water is added while mixing until swelling is complete. The resulting solution is adjusted to pH 5.0 with sodium hydroxide 1 N and diluted with the rest of the purified water ad 100 g.

Example 8 : TOPICAL CREAM

2% topical cream

To a solution of 200 mg hydroxypropyl β-cyclodextrine in purified water is added 20 mg of A.I. 1 and/or 0.2 mg A.I. 2 while stirring. Hydrochloric acid is added until complete dissolution and next sodium hydroxide is added until pH 6.0. While stirring, 50 mg glycerol and 35 mg polysorbate 60 are added and the mixture is heated to 70°C. The resulting mixture is added to a mixture of 100 mg mineral oil, 20 mg stearyl alcohol, 20 mg cetyl alcohol, 20 mg glycerol monostearate and 15 mg sorbate 60 having a

temperature of 70°C while mixing slowly. After cooling down to below 25°C, the rest of the purified water q.s. ad 1 g is added and the mixture is mixed to homogenous.

In a similar way a 1%, a 3% and a 5% topical cream containing the following ingredients were prepared :

Ingredient	Quantity		
	1% topical cream	*3% topical cream*	*5% topical cream*
Liarozole hydrochloride	11.18 mg	33.54 mg	55.91 mg
Hydroxypropyl β-cyclodextrine	75 mg	75 mg	75 mg
Cetyl alcohol	15 mg	15 mg	15 mg
Stearyl alcohol	15 mg	15 mg	15 mg
Liquid paraffin	100 mg	100 mg	100 mg
Glyceryl stearate	30 mg	30 mg	30 mg
Sorbitan monostearate	15 mg	15 mg	15 mg
Polysorbate 60	15 mg	15 mg	15 mg
Propylene glycol	150 µl	150 µl	150 µl
Carbomer 1382	1.5 mg	1.5 mg	1.5 mg
Benzylalcohol	10 mg	10 mg	10 mg
Diazolidinyl urea	3 mg	3 mg	3 mg
Purified water q.s. ad	1000 mg	1000 mg	1000 mg

The above-mentioned 1%, 3% and 5% topical creams may be supplemented with 0.1 mg, 0.3 mg and 0.5 mg calcitriol respectively.

Example 9 : SUPPOSITORIES

3 g A.I. 1 and/or 0.03 g A.I. 2 was dissolved in a solution of 3 g 2,3-dihydroxy-butanedioic acid in 25 ml polyethylene glycol 400. 12 G surfactant and triglycerides q.s. ad 300 g were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37~38°C to form 100 suppositories each containing 30 mg of the active ingredient.

B) Biological Example

Example 10 : Metabolism of calcitriol by human foreskin keratinocytes, pig kidney cells and human hepatoma cells

The dermal and epidermal tissues of human foreskin was cut in 0.5 cm^2 pieces and incubated overnight at 4°C in 10 ml phosphate buffer (PBS) without calcium and magnesium, containing 2 ml Dispase II (a protease supplied by Boehringer Mannheim at an activity of 24U/ml). After incubation, the tissue was placed in 15 ml trypsin (0.125%) - EDTA (0.01%) and the epidermal fraction was carefully lifted with a pincet. By gently scraping the dermis, the adherent keratinocytes were released from the tissue into the trypsin solution. After removal of all dermal parts, the remaining solution (containing the keratinocytes and the stratum corneum sheets) was incubated for 20 min. at 37°C. After filtration, the filter was washed once with keratinocyte-free medium (SFM) and fetal calf serum was added to the filtrate to reach a final concentration of 10% (inactivation of the trypsin-EDTA). After centrifugation of the cell suspension (10 min. at 1000 rpm), the cells were counted and plated in keratinocyte-SFM (supplemented with an antibiotic-antimycotic mix and 2 µg gentamycin/ml) at a cell density of 3.10^6 cells/75 cm^2 tissue culture flask and incubated at 37°C in a 5%-CO_2 humidified atmosphere. After 2-3 days of cultivation, the medium was replaced by antibiotic-antimycotic-free medium. After reaching confluence, cells were trypsinized and, after inactivation of the remaining trypsine by fetal calf serum, seeded in 6-well-plates at a cell density of 1.10^5 cells/ml keratinocyte-SFM. The medium was refreshed every 2-3 days and 16 hours before the onset of the experiment. At the start of the experiment, the medium was again replaced by 2 ml of keratinocyte-SFM. The calcitriol metabolism was initiated by adding 0.1 µCi 1α,25-[26,27-^{3}H]-dihydroxyvitamin-D_3 in 10 µl ethanol and 2 µl drug and/or solvent (DMSO). At the end of a three hour incubation period, the medium was transferred into a brown coloured test tube containing 3 ml chloroform and 0.5 ml 10% formic acid. The cells were trypsinized with 0.5 ml trypsine (0.125%) - EDTA (0.01%) and after 15 min. incubation at room temperature combined with the medium-chloroform mixture. The 6-well plates were washed twice with 1.5 ml methanol which was added to the extraction tube. After 20 min. of extraction, the chloroform layer was separated from the water layer by centrifugation (10 min. at 2400 rpm) and the water layer reextracted with 3 ml chloroform. After evaporation of the chlorofrom under a stream of nitrogen, calcitriol and its metabolites were dissolved in 0.2 ml n-hexane:isopropanol (90:10) and analyzed by HPLC.

Pig kidney cells collected from one 75 cm^2 tissue culture flask were suspended in 160 ml Medium 199 (a synthetic culture medium supplied by Life-Technologies) containing 3%

foetal calf serum (FCS). Two ml of the cell suspension were seeded in 6-well plates and incubated at 37°C in a humidified 5% CO_2 atmosphere. The medium was refreshed every 2-3 days. At the onset of the experiment, confluent cultures were washed with phosphate buffer (PBS) without calcium and magnesium and refreshed with with 2 ml medium 199 without serum. The metabolism of 1α,25-[26,27-^{3}H]-dihydroxyvitamin-D_3 was studied as described for the human foreskin keratinocytes.

Human hepatoma cells were grown at 37°C (in a CO_2 incubator) in 2 ml REGA-3 medium (a synthetic culture medium supplied by Life-Technologies) supplemented with 5% FCS. After 24 h of growth, 1.25 µCi [^{14}C]-acetate, drug and/or DMSO were added and cells were grown for another 24 h. At the end of the incubation period, cells were collected by centrifugation, washed with physiological saline and resuspended in 1 ml H_2O and 1 ml 15% KOH in 90% ethanol. The metabolism of 1α,25-[26,27-^{3}H]-dihydroxyvitamin-D_3 was studied as described for the human foreskin keratinocytes.

After effecting the above test procedures, IC_{50} values for the compounds of formula (I) were calculated by conventional techniques. Table 1 summarizes the obtained IC_{50} values for some of the subject compounds.

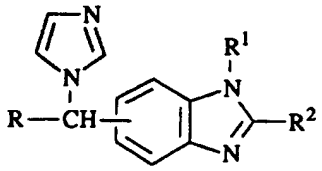
Table 1

	IC_{50}-values (µM)		
	Human foreskin keratinocytes	Pig kidney cells	Human hepatoma cells
liarozole . HCl	2.1	1.3	0.4
(+)-liarozole . HCl	2.9	1.8	0.9
(-)-liarozole . HCl	1.8	1.0	0.3

The data in Table 1 illustrate the inhibitory activity of the compounds of formula (I) on the metabolic degradation of calcitriol.

Claims

1. The use of a (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazole for the manufacture of a medicament for treating a pathological condition which is beneficially influenced by inhibiting the metabolic degradation of calcitriol, said benzimidazole having the formula



(I),

wherein

R is hydrogen; C_{1-10}alkyl; C_{3-7}cycloalkyl; Ar^1 or Ar^1-C_{1-6}alkyl;

R^1 is hydrogen; C_{3-7}cycloalkyl; Ar^1; C_{1-10}alkyl; C_{1-6}alkyl substituted with Ar^1 or C_{3-7}cycloalkyl; hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{3-6}alkenyloxy optionally substituted with Ar^2; C_{3-6}alkynyloxy optionally substituted with Ar^2; or Ar^1-oxy;

R^2 is hydrogen; halo; C_{1-10}alkyl; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; Ar^1; quinolinyl; indolinyl; C_{1-6}alkyl substituted with Ar^1, C_{3-7}cycloalkyl, quinolinyl, indolinyl or hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{3-6}alkenyl optionally substituted with Ar^1; Ar^2-oxy; C_{1-6}alkyloxycarbonyl; carboxyl; C_{1-6}alkylcarbonyl; Ar^1-carbonyl or Ar^1-(CHOH)-;

each Ar^1 independently is phenyl, substituted phenyl, pyridinyl, aminopyridinyl, imidazolyl, thienyl, halothienyl, furanyl, halofuranyl or thiazolyl;

each Ar^2 independently is phenyl or substituted phenyl;

in Ar^1 and Ar^2 said substituted phenyl represents phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, amino, mono- and di(C_{1-6}alkyl)amino, nitro, carboxyl, formyl and C_{1-6}alkyloxycarbonyl,

a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

2. The use of a (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazole as claimed in claim 1 wherein

R is phenyl or substituted phenyl;

R^1 is hydrogen or C_{1-6}alkyl;

R^2 is hydrogen; halo; C_{1-6}alkyl; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; phenyl; substituted phenyl; C_{1-6}alkyl substituted with phenyl or substituted phenyl;
said substituted phenyl represents phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy and cyano.

3. The use of a (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazole as claimed in claim 1 wherein the compound of formula (I) is a 5-[(3-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-benzimidazole.

4. The use of a (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazole as claimed in claim 1 wherein the compound of formula (I) is used in combination with calcitriol or a prodrug thereof.

5. The use of a (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazole as claimed in claim 4 wherein the pathological condition is a keratinization disorder.

6. The use of a (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazole as claimed in claim 5 wherein the pathological condition is psoriasis.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) an effective amount of calcitriol or a prodrug thereof, and (b) an effective amount of a compound of formula (I) as described in any one of claims 1 to 3.

8. A pharmaceutical composition as claimed in claim 7 wherein the active ingredients are (a) calcitriol, and (b) a 5-[(3-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-benzimidazole.

9. A pharmaceutical composition as claimed in claim 7 or 8 wherein the composition is adapted for topical administration.

10. A pharmaceutical composition as claimed in claim 9 wherein the composition comprises from 0.005 to 0.5% w/w calcitriol and from 0.05 to 5% of a 5-[(3-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-benzimidazole, in a semi-solid or liquid diluent or carrier.

11. A pharmaceutical composition as claimed in claim 10 wherein the composition comprises from 0.01 to 0.1% w/w calcitriol.

12. A process for preparing a composition as claimed in any of claims 7 to 11, characterized in that an effective amount of calcitriol or a prodrug thereof and an effective amount of a compound of formula (I) as described in any one of claims 1 to 3 are combined in intimate admixture with the pharmaceutically acceptable carrier.

13. A product containing (a) a pharmaceutical composition containing an effective amount of calcitriol or a prodrug thereof and a pharmaceutical acceptable carrier, and (b) a pharmaceutical composition containing an effective amount of a compound of formula (I) as described in any one of claims 1 to 3, and a pharmaceutical acceptable carrier, as a combined preparation for simultaneous, separate or sequential use in the treatment of pathological conditions which are beneficially influenced by inhibiting the metabolic degradation of calcitriol.

14. A product according to claim 13 wherein the product contains (a) a pharmaceutical composition containing calcitriol, and (b) a pharmaceutical composition containing a 5-[(3-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-benzimidazole.

15. A product according to claim 14 wherein the product is adapted for topical administration.

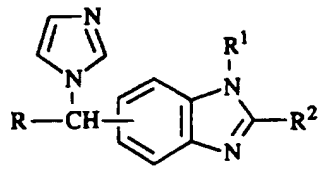
16. A product according to claim 15 wherein the product contains (a) a pharmaceutical composition containing from 0.005 to 0.5% w/w calcitriol, and (b) a pharmaceutical composition containing from 0.05 to 5% of a 5-[(3-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-benzimidazole.

17. A product according to claim 16 wherein the product contains a pharmaceutical composition containing from 0.01 to 0.1% w/w calcitriol.

18. A product according to any one of claims 13 or 17 as a combined preparation for simultaneous, separate or sequential use in the treatment of keratinization disorders.

19. A product according to any one of claims 13 or 17 as a combined preparation for simultaneous, separate or sequential use in the treatment of psoriasis.

20. A method of treating patients suffering from a pathological condition which is beneficially influenced by inhibiting the metabolic degradation of calcitriol, comprising the administration to said patients of an effective amount of a (1*H*-imidazol-1-yl)methyl-1*H*-benzimidazole, said benzimidazole having the formula



(I),

wherein

R is hydrogen; C_{1-10}alkyl; C_{3-7}cycloalkyl; Ar^1 or Ar^1-C_{1-6}alkyl;

R^1 is hydrogen; C_{3-7}cycloalkyl; Ar^1; C_{1-10}alkyl; C_{1-6}alkyl substituted with Ar^1 or C_{3-7}cycloalkyl; hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{3-6}alkenyloxy optionally substituted with Ar^2; C_{3-6}alkynyloxy optionally substituted with Ar^2; or Ar^1-oxy;

R^2 is hydrogen; halo; C_{1-10}alkyl; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; Ar^1; quinolinyl; indolinyl; C_{1-6}alkyl substituted with Ar^1, C_{3-7}cycloalkyl, quinolinyl, indolinyl or hydroxy; C_{1-10}alkyloxy; C_{1-6}alkyloxy substituted with Ar^1 or C_{3-7}cycloalkyl; C_{3-6}alkenyl optionally substituted with Ar^1; Ar^2-oxy; C_{1-6}alkyloxycarbonyl; carboxyl; C_{1-6}alkylcarbonyl; Ar^1-carbonyl or Ar^1-(CHOH)-;

each Ar^1 independently is phenyl, substituted phenyl, pyridinyl, aminopyridinyl, imidazolyl, thienyl, halothienyl, furanyl, halofuranyl or thiazolyl;

each Ar^2 independently is phenyl or substituted phenyl;

in Ar^1 and Ar^2 said substituted phenyl represents phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, amino, mono- and di(C_{1-6}alkyl)amino, nitro, carboxyl, formyl and C_{1-6}alkyloxycarbonyl,

a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

21. A method according to claim 20 wherein

R is phenyl or substituted phenyl;

R^1 is hydrogen or C_{1-6}alkyl;

R^2 is hydrogen; halo; C_{1-6}alkyl; C_{1-4}alkyl substituted with up to 4 halo atoms; C_{3-7}cycloalkyl; phenyl; substituted phenyl; C_{1-6}alkyl substituted with phenyl or substituted phenyl;

said substituted phenyl represents phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy and cyano.

22. A method according to claim 21 wherein the compound of formula (I) is a 5-[(3-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-benzimidazole.

23. A method according to claim 20 wherein the compound of formula (I) is administered in combination with an effective amount of calcitriol or a prodrug thereof.

24. A method according to claim 23 wherein the pathological condition is a keratinization disorder.

25. A method according to claim 24 wherein the pathological condition is psoriasis.

INTERNATIONAL SEARCH REPORT

Interr. ··· ·al Application No
PCT/EP 95/05172

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CELL BIOLOGY INTERNATIONAL, vol. 18, no. 5, 1994 page 558 XP 000568167 G. DANEELS ET AL. 'Modulation of Ca2+-induced normal human keratinocyte differentation by liarozole HCl.' * abstract * ---	1-3,5,6, 20-22
X	PROC. WORKSHOP VITAM. D, vol. 9, 1994 pages 186-187, XP 000568192 J. ZHAO ET AL. 'Potentialization of vitamin D (analogs) by cytochrome P-450 enzyme inhibitors is analog- and cell-type specific.' see the whole document --- -/--	1-4,7,8, 12,20-23

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 April 1996	19.04.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Klaver, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/EP 95/05172

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NEW ENGL. J. MED., vol. 328, no. 25, 1993 pages 1845-1846, XP 000568134 G.G. KRUEGER ET AL. 'Psoriasis therapy - observational or rational?' see the whole document ---	1-3,5,6, 20-22
X	EP,A,0 371 559 (JANSSEN PHARMACEUTICA) 6 June 1990 cited in the application see page 12, line 33 - line 46; table 2 ---	1-3,5,6, 20-22
P,X	WO,A,95 22540 (JANSSEN PHARMACEUTICA) 24 August 1995 cited in the application see claims ---	1-3,5,6, 20-22
P,X	BR. J. DERMATOL., vol. 133, no. 3, 1995 pages 426-432, XP 000568170 P. DOCKX ET AL. 'Inhibition of the metabolism of endogenous retinoic acid as treatment for severe psoriasis: an open study with oral liarozole' see the whole document -----	1-3,5,6, 20-22

1

INTERNATIONAL SEARCH REPORT

national application No.

PCT/EP 95/05172

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 20-25 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/EP 95/05172

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-371559	06-06-90	AT-T-	112681	15-10-94
		AU-B-	630579	29-10-92
		AU-B-	1071692	19-03-92
		AU-B-	623454	14-05-92
		AU-B-	4564889	07-06-90
		CA-A-	2002859	29-05-90
		DE-D-	68918809	17-11-94
		DE-T-	68918809	23-03-95
		EP-A-	0609963	10-08-94
		ES-T-	2065369	16-02-95
		HK-A-	114895	21-07-95
		IL-A-	92487	29-12-94
		JP-A-	3020273	29-01-91
		PT-B-	92449	18-07-95
		US-A-	5420147	30-05-95
		US-A-	5500435	19-03-96
		US-A-	5157046	20-10-92
		US-A-	5342957	30-08-94
WO-A-9522540	24-08-95	AU-B-	1578795	04-09-95